Update on Diabetes Treatment: Oral Agents and Non-Insulin Injectables, Insulin and Insulin Pumps

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Disclaimer

I do not have any significant financial relationships to disclose.

Objectives

- Review basic types of diabetes
- Discuss Non-Insulin Treatment Options (oral and injectables)
- Understand difference in insulin products
- Discuss advantages/disadvantages of various treatment options
- Review key points of insulin pump therapy
- Apply information learned to a case study

Types of Diabetes

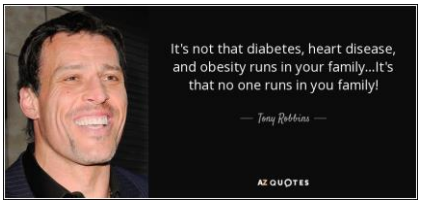
- Type 1:
  - polygenic (mutation in many genes)
  - autoimmune disease
  - beta cells destroyed-no insulin produced
  - usually diagnosed in childhood, adolescence or early adulthood (not always –can be diagnosed at any age)
- Gestational diabetes:
  - develops during pregnancy
  - insulin resistance develops w/ fluctuating hormones of pregnancy
  - usually resolves after delivery but high risk for developing type 2 later

Types of Diabetes, cont.

- Type 2:
  - polygenic
  - insulin resistance; often excess amount of insulin produced
  - usually overweight
  - generally accompanied by HTN and hyperlipidemia
  - burns out beta cells
- Latent Autoimmune Diabetes in Adults (LADA):
  - polygenic
  - Type 1.5
  - slower destruction of beta cells
  - often treated as type 2 at onset

Types of Diabetes, cont.

- Maturity Onset Diabetes of the Young (MODY):
  - monogenic (one gene mutation involved)
  - occurs during adolescence or early adulthood
  - often undiagnosed until later in life
  - not typical type 2 presentation
- Neonatal Diabetes Mellitus (NDM):
  - monogenic
  - occurs during first 6 month
  - 50% transient but can reappear later in life



Normal Glucose Homeostasis

- Major source of the body's energy
- Ingested and absorbed through wall of GI tract
- Stimulates release of glucagon-like polypeptide-1 (GLP-1)
- GLP-1 receptors in pancreatic islets → secretion of insulin + suppression of glucagon
- Glucose stored in muscle and liver
- Balance insulin/glucagon secretion maintains adequate energy supplies and normal glucose levels

Diagnosing Diabetes

Goals of therapy

	Most adults	Pediatric age group	Pregestational type 1 or 2	Gestational DM
A1c	<7%	<7.5%	6-6.5%	
Pre-prandial	80-130 mg/dl	90-130 mg/dl	< 90mg/dl	≤ 95mg/dl
Post-prandial	< 180 mg/dl		1 hr :130-140 mg/dl 2 hrs: ≤ 120 mg/dl	1 hr: ≤ 140 mg/dl 2 hrs:≤ 120mg/dl
Bedtime		90- 150 mg/dl		

A1c to eAG conversion

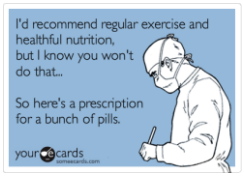
28.7 X A1c - 46.7= eAG

A1c %	eAG mg/dl
6	126
7	154
8	183
9	212
10	240
11	269
12	298

A1c

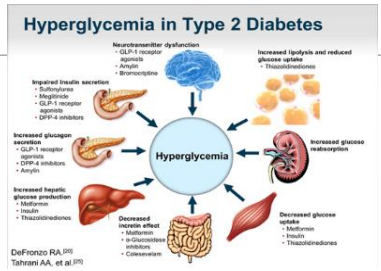
- What's the value of A1c?
- Does A1c value help us with therapy decisions?
- A1c >=10%: fasting glucose plays a more important role
- A1c <=8%: post prandial glucose major factor

Diabetes Self Management



Oral and Non-insulin Injectable Medication

- Treatment for Type 2; LADA in early stages; MODY; gestational (limited)
- First line treatment options:
  AACE (American Association of Clinical Endocrinologists) and ACE (American College of Endocrinologists) algorithm differs slightly from ADA (American Diabetes Association) algorithm
- Agree with progression of therapy (every 3 months to goal)
  Monotherapy → Dual therapy → Triple Therapy → Combo with insulin
- Pregnancy options: metformin; glyburide (maybe)



Oral Medications (9 classes)

Most commonly used:
- Biguanides
- SGLT-2 Inhibitors
- DPP-4 Inhibitors
- TZDs
- Sulfonylureas
- Meglitinides
- Dopamine-2 agonists

Rarely used:
- α-Glucosidase Inhibitors
- Bile acid Sequestrant
- Dopamine-2 agonists

Biguanides

- ADA monotherapy AACE/ACE- one of choices for monotherapy
- Mechanism of action:
  ↑ sensitivity of muscle cells to insulin
  ↓ amount of sugar produced by cells in the liver
  delays absorption of sugar from the intestines → bloodstream
- One commercially available:
  Metformin (Glucophage, Foramet, Glumetza)

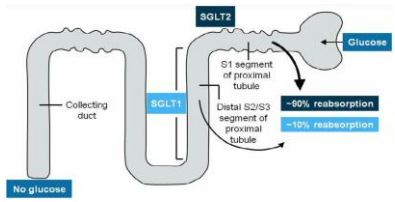
Biguanides

Advantages	Disadvantages
Extensive experience	GI side effects
No hypoglycemia	Vitamin B12 deficiency
Decrease in CVD events	Contraindications: CKD
Low cost	
Weight neutral	
Once or twice daily dosing	
? Benefit in type 1	

Biguanides

- Start low and go slow
  - 500 mg with largest meal of day to start
  - titrate up to maximum effective dose of 2000mg/day
- Take with food to decrease GI upset
- Lowers fasting and basal glucose
- Lowers A1c 1-2 %

Sodium-glucose co-transporter 2 (SGLT2) inhibitors



Sodium-glucose co-transporter 2 (SGLT2) inhibitors

SGLT2: receptor that facilitates glucose reabsorption in the kidney

- SGLT2 inhibitors:
  - block reabsorption of glucose in the kidney
  - ↑ glucose excretion
  - ↓ blood glucose levels

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

3 currently available:

- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

Advantages	Disadvantages
No hypoglycemia	Genitourinary infections
Weight loss	Polyuria
Decrease BP	Volume depletion/hypotension/dizziness
Effective at all stages of type 2	Increase LDL-C
Empagliflozin- CVD benefit	Transient increase creatinine
? benefit in type 1	DKA
Once daily dosing	High cost

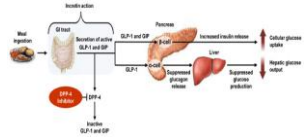
Sodium-glucose co-transporter 2 (SGLT2) inhibitors

- Canagliflozin take before 1st meal of day
- Others daily with or without food
- Lowers post prandial glucose
- Watch for dizziness/orthostatic hypotension
- Maintain adequate hydration
- Lower A1c 0.4-0.8%

Dipeptidyl peptidase-4 (DPP-4) inhibitors

Glucose-dependent insulin-releasing polypeptide (GIP) and GLP-1 secreted in response to food ingestion and potentiate the glucose-induced insulin response

Rapidly degraded by the enzyme DPP-4; causing inactivation of the majority of GLP-1 and GIP



Dipeptidyl peptidase-4 (DPP-4) inhibitors

- Inhibit DPP-4 activity

↑ postprandial active incretin (GLP-1, GIP) concentrations

↑ insulin secretion (glucose dependent)

↓ glucagon secretion (glucose dependent)

Dipeptidyl peptidase-4 (DPP-4) inhibitors

4 commercially available:

Sitaglitptin (Januvia)

Saxagliptin (Onglyza)

Linagliptin (Tradjenta)

Alogliptin (Nesina)

Dipeptidyl peptidase-4 (DPP-4) inhibitors

Advantages	Disadvantages
No hypoglycemia	Pancreatitis
Well tolerated	Angioedema/urticarial and other immune-medicated dermatological effects
Weight neutral	High cost
Once daily dosing	

Dipeptidyl peptidase-4 (DPP-4) inhibitors

- May take with or without food
- Lower post prandial blood glucose
- Decrease A1c by 0.4-0.8%

Aalpha-Glucosidase Inhibitors

Alpha-Glucosidase Inhibitors

- Delay breakdown of complex carbohydrates into glucose
- Absorption of glucose delayed in distal portion of small intestine
- 2 currently available:
  - Miglitol (Glyset)
  - Acarbose (Precose)

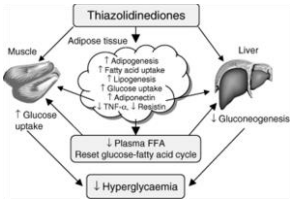
Alpha-Glucosidase Inhibitors

Advantages	Disadvantages
No hypoglycemia	Gastrointestinal
Decrease post prandial excursions	Moderate cost
Non systemic	Frequent dosing schedule
Weight neutral	

Alpha-Glucosidase Inhibitors

- Take with first bite of food; hold if not eating
- Lower post prandial glucose
- Initial dose for both 25 mg tid; increase as tolerated for post prandial target with maximum dose 100mg tid
- Regular sugar (sucrose) ineffective for hypo
- Use oral glucose (dextrose) for hypo if on combo medication
- Lower A1c 0.5-0.8%

Thiazolidinediones (Glitazones or TZDs)



Thiazolidinediones (Glitazones or TZDs)

- Bind avidly to peroxisome proliferator-activated receptor gamma (PPARY)
- Improve insulin sensitivity
- Change in fat metabolism ⟶ substantial reduction in circulating free fatty acids
- 2 commercially available:
  - Pioglitazone (Actos)
  - Rosiglitazone (Avandia)
- Lower A1c 0.5-1.4 %

Thiazolidinediones (Glitazones or TZDs)

Advantages	Disadvantages
No hypoglycemia	Increase weight
Increase HDL-c	Edema/heart failure
Decrease triglycerides (pio)	Increase fracture risk
May reduce stroke risk	Increase LDL-C (rosi)
Low cost	8-12 weeks to see effect
Once (pio + rosi) or twice (rosi) daily	

Thiazolidinediones (Glitazones or TZDs)

- Take with or without food
- Lower fasting and basal blood glucose
- Watch for fluid retention
- Dosing : Rosiglitazone 4- 8mg daily in single or divided dose
  Pioglitazone 15-45mg daily as single dose
- Lower A1c 0.5-1.4%

Sulfonylureas

- Close KATP channels on Beta cell plasma membrane
- ↑ insulin secretion
- 3 commercially available products
  Glyburide (Micronase, Diabeta, Glynase)
  Glipizide (Glucotrol, Glucotrol XL)
  Glimepiride (Amaryl)

Sulfonylureas

Advantages	Disadvantages
Extensive experience	Weight gain
Low cost	High risk of hypoglycemia

Sulfonylureas

- Take about 30 minutes before meal
- Do not skip meals
- Lower fasting and basal glucose
- Lower A1c 1-2 %

Meglitinide (glinides)

- Close KATP channels on Beta cell plasma membrane
- ↑ insulin secretion
- 2 commercially available :
  Repaglinide (Prandin)
  Nateglinide (Starlix)

Meglitinide (glinides)

Advantages	Disadvantages
Decrease postprandial excursions	Hypoglycemia
Dosing flexibility	Weight gain
	Frequent dosing schedule
	Moderate cost

Meglitinide (glinides)

- Take just before meal
- Lower post prandial glucose
- Extent of insulin release glucose dependent; diminishes at low glucose levels
- Dosed with each meal and maybe snack
  Hold dose if not eating
- Lower A1c 0.5-1.5%

Bile acid Sequestrant

- Binds bile acid in intestinal tract
- Increases hepatic bile production
- Exact mechanism of blood glucose lowering unknown
  ? Decrease hepatic glucose production
  ? Increase incretin levels
- Only one with a DM indication : Colesvelam (Welchol)

Bile acid Sequestrant

Advantages	Disadvantages
No hypoglycemia	Constipation
Decrease LDL-C	Increase triglycerides
CVD benefit	May decrease absorption of other meds
Weight neutral	Cost

Bile acid Sequestrant

- Lower post prandial glucose
- Dosing: 3 tablets bid with meal or 6 tablets daily with meal
- Lowers A1c 0.5%

Dopamine-2 agonists

- Activates dopamine receptors
- Modulated hypothalamic regulation of metabolism
- Increases insulin sensitivity
- One commercially available for tx DM:
  bromocriptine (Cycloset)

Dopamine-2 agonists

Advantages	Disadvantages
No hypoglycemia	Hypotension
? Decreased CVD events	Nausea
Weight neutral	Fatigue
	Rhinitis
	Cost

Dopamine-2 agonists

- Watch for dizziness/syncope
- Effects on blood glucose unknown
- Lowers A1c 0.1%

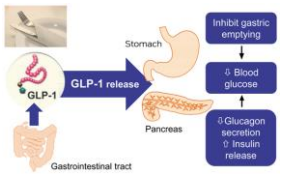
Non-insulin injectables

2 categories:

GLP-1 receptor agonists

Amylin mimetics

GLP-1 agonists



GLP-1 agonists

- Activate GLP-1 receptors
- ↑ insulin secretion (glucose dependent)
- ↓glucagon secretion (glucose dependent)
- slow gastric emptying time
- ↑satiety

GLP-1 agonists

Commercially available products) :

Exenatide (Byetta, Bydureon)

Dulaglutide (Trulicity)

Liraglutide (Victoza)

Lixisenatide (Adlyxin)

Semaglutide (Ozempic)

Lixisenatide and semaglutide also available in combination with basal insulin

GLP-1 agonists

Advantages	Disadvantages
Weight loss	GI side effects
Liraglutide CHF/CVD benefit	Cost
Injectable	Pancreatitis ? Thyroid cancer
	Dulaglutide ? First degree heart block
	Injectable

GLP-1 agonists

- Lower fasting and post prandial glucose
- A1c lowering 0.5-1.3%

Amylin Mimetics

- Activates amylin receptors
- ↓ glucagon secretion
- slows gastric emptying
- ↑ satiety
- One commercially available
  Pramlintide (Symlin)

Amylin Mimetics

Advantages	Disadvantages
Decrease weight	Cost
Decrease post prandial excursions	GI side effects
	Frequent dosing schedule
	Increased risk of hypoglycemia

Amylin Mimetics

- Indicated for Type 1 or Type 2 patients with DM on insulin
- Associated with SEVERE hypoglycemia in Type 1 patients within 3 hours of administration
- Do not mix with insulin in same syringe

Insulin

- Glucose in plasma of individual without DM stays within a normal range despite large fluctuations in nutritional intake (Thanksgiving) and physical activity (marathon)
- Precise balance exists between insulin secretion from pancreatic Beta cells and insulin action on sensitive tissues, primarily adipose tissue, liver and muscle exists

After individual without DM eats, plasma glucose concentration:

increases rapidly

peaks in 30-60 min

returns to basal conc. within 2-3 h

Bolus insulin

- Large peak of endogenous insulin in response to increase glucose
- Maximum effect 1 hours; wanes in 2-3 hours
- Approximately 50% of body's insulin secretion
- Commercial products attempt to mimic

Bolus Insulin Profiles

Insulin	Onset of Action	Peak Action	Duration of Action
Lispro (Humalog)	≈ 15 min	0.5-2 hours	3-5 hours
Aspart (NovoLog)	≈ 15 min	0.5-2 hours	3-5 hours
Aspart (Fiasp)	2.5 min	0.5-2 hours	3-5 hours
Glulisine (Apidra)	12-24 min	0.5-2 hours	3-5 hours
rDNA human powder (Afrezza)	12-24 min	50-60 min	2-3 hours
Regular (Novolin N, Humulin R)	30-60 min	2-5 hours	5-8 hours

Basal Insulin

- Somewhat constant secretion of endogenous insulin over 24-hr period
- Not related to food intake
- Relatively constant rate- no pronounced peak effect
- Suppress glucose production between meals
- Regulates glucose output from liver
- 50% of body's insulin secretion
- Commercial products attempt to mimic

Basal Insulin Profiles

Insulin	Onset of Action	Peak Action	Duration off Action
NPH (Humulin N, Novolin N)	2-4 hours	4-10 hours (median 8 hours)	10-16 hours
Glargine (Basaglar, Lantus)	1-1.5 hours	No peak	20-24 hours
Detemir (Levemir)	1-2 hours	Slight 6-8 hours	Up to 24 hours
Degludec (Tresiba)	30-90 min	No peak	42 hours Reaches steady state in 3-4 days

Pre-Mixed Insulin

Insulin	Onset of Action	Peak Action	Duration of Action
Lispro protamine+ Lispro (Humalog Mix 75/25, 50/50)	15-30 min	Dual 1-4 hours 6-8 hours	10-16 hours
Aspart protamine+aspart (NovoLog Mix 70/30)	10-20 min	Dual 1-4 hours 6-8 hours	18-24 hours
NPH + Regular (Humulin 50/50, 70/30, Novolin 70/30)	30-60 min	Dual 0.8-2 hours 6-10 hours	18-24 hours

Concentrated Insulin with alternate profiles

Insulin	Onset of Action	Peak Action	Duration of Action
Glargine concentrated 300 units/ml (Toujeo)	6 hours	12 hours	≈ 24 hours
Regular U-500 (Humulin R U-500)	15-30 min	4-8 hours	13-24 hours

Insulin Pumps

- Deliver rapid- or short-acting insulin 24 hours a day through a catheter placed under the skin
- Insulin doses are separated into:

  Basal rates-continuous over 24 hours

  Bolus doses:

  Cover carbohydrate taken intake

  Correct high blood glucose

Insulin Pumps

Insulin Pumps

Advantages	Disadvantages
Eliminate individual injections	Weight gain
Greater accuracy	DKA-if catheter kinks or comes out
Reduction in severe hypo	Learning curve
Allows for variable basal needs	May limit activity
Eliminate unpredictable effects of "basal" insulin products	
More flexible dining schedule	

Signs of hypoglycemia

Shakiness

Hunger

Dizziness

Headache

Anxiety

Moodiness

What is hypoglycemia?

ADA 2017 Standards of Care:

Hypoglycemia is < 70 mg/dl

Severe hypoglycemia: < 54 mg/dl

Treating hypoglycemia

Rule of 15

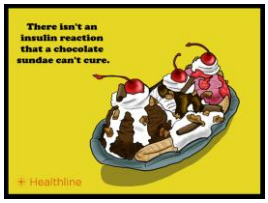
Fast acting carbohydrate 15 g

Wait 15 minutes

Recheck; if still < 70 mg/dl retreat; if > 70 mg/dl follow with complex carbohydrate

Treatment examples

Fast acting carb	Complex carb
4 ounces juice	Peanut butter crackers
4 ounces regular soda	½ turkey sandwich
3 or 4 Dextrose tablets	100 calorie yogurt
7-8 gummy or regular Life Savers	
2 tbsp. raisins	
15 Skittles	
Glucagon	



Some Helpful Tools

Case Study

Betty is a 66 year young female patient referred to you for diabetes education

PMH:

Type 2 DM (diagnosed age 55)

HTN

Allergies: sulfa, PCN

Family history: Mother diabetes, HTN, Stroke age 67; expired age 80

Father: CAD; MI and expired age 75

Social history: Married; 2 adult children and 4 grandchildren

Retired; active at local YMCA (bingo)

Case Study continued

Medications:

Lisinopril 10 mg po daily

HCTZ 12.5 mg po daily

Metformin 500 mg po bid (breakfast and supper)

Lantus Insulin 40 units sc hs

Atorvastatin 10 mg po daily

Vitals:

Ht: 63 inches Wt: 160 lbs. BP: 120/60 A1c: 8.5% (eAG 197 mg/dl)

Case Study continued

What do you think about her current medication regimen?

What's driving her A1c value more; fasting or post prandial?

What do you think her A1c goal should be?

Is there any more information you would like?

Case Study continued

BS diary:

	Sunday	Monday	Tues.	Wed.	Thurs.	Friday	Sat.
Fasting	140	135	142	136	145	146	132
Pre-supper	155	160	145	137	150	148	138
2 hrs. post supper	215	230	200	192	210	203	198

Case Study continued

Maximize metformin to 2000 mg/day

Teach healthy eating

Consider agents to reduce post-prandial excursions (assume cost not a barrier)

Case Study continued

You saw Betty for several educational visits

She increased her physical activity

Made significant changes to her food intake

Medications now include:

Metformin 1000 mg po bid

Lantus 40 units sc hs

Jardiance 10 mg po daily

Case Study continued

She contacts you in one year

A1C now 6.9%

Wt: 140 lbs.

She's done great except….she can no longer afford her Lantus insulin or Jardiance (they are Tier 3 and 4 respectively and last year put her in the donut hole in August)

She has told her PCP but he isn't really listening

Case continued

You need to advocate for her

What can you suggest as alternative, affordable therapy?

Questions

References

AACE/ACE Comprehensive Type 2 Algorithm 2017

American Diabetes Association Standards of Medical Care in Diabetes 2017

Lexi Comp on line: Individual drug Monographs

http://integrateddiabetes.com/insulin-pump-comparisons/

Contact Information

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